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November 3, 2004

Mail Stop Amendment Commissioner for Patents Post Office Box 1450 Alexandria, VA 22313-1450

Re: U.S. Patent Application No. 10/718,765

For: Use Of Creatine Or Creatine Analogs for the Treatment

of Diseases of the Nervous System Inventors: Kaddurah-Daouk, Rima et al.

Filed: November 21, 2003

Our Ref. No.: AVZ-001CPUSCN2

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

- 1. Information Disclosure Statement;
- 2. PTO Form SB/08;
- 3. Copy of the publication cited in PTO Form SB/08 (1); and
- 4. A Return Postcard.

No additional costs are believed to be due in connection with the filing of this Information Disclosure Statement. However, please charge any necessary fees in connection with the enclosed statement to our Deposit Order Account No. 12-0080. For this purpose, a duplicate of this sheet is attached.

I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: MS Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on:

November 3, 2004

Date

Meriden C. Arnold, Registration No. 52,568

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

Merideth C. Arnold, Esq Registration No. 52,568

Attorney for Applicants



## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Fre the application of: Kaddurah-Daouk, Rima, et al.

Serial No.: 10/718,765

Filed: November 21, 2003

For: Use of Creatine or Creatine Analogs for the

Treatment of Diseases of the Nervous System

Attorney Docket No.: AVZ-001CPUSCN2

Group Art Unit: 1639

Examiner: Not Yet Assigned

Mail Stop Amendment Commissioner for Patents Post Office Box 1450 Alexandria, VA 22313-1450

## Certificate of First Class Mailing (37 CFR §1.8(a))

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November 3, 2004

Date of Signature and of Mail Deposit

By: ✓

Merideth C. Arnold, Esq.

Registration No. 52,568 Attorney for Applicants

## INFORMATION DISCLOSURE STATEMENT

Dear Sir:

For the Examiner's convenience in reviewing this continuation application, Applicants submit a consolidated PTO Form SB/08, listing all references cited during the prosecution of the parent application. References A1-A4, A6-A14, and B1-H2 were previously cited and submitted to the Office in U.S. Application Serial No. 08/853,174, filed May 7, 1997 (Atty. Docket No. AVZ-001CPUS), of which this application is a continuation and to which this application claims priority. In accordance with 37 CFR §1.98(d), these references are not enclosed herewith, but will be provided upon request. In addition, this Information Disclosure

Serial Number: 10/718,765 Page -2-Group Art Unit: 1639

Statement presents reference A5, not previously submitted to the Office, which is enclosed herewith in accordance with 37 CFR §1.97.

This statement is not to be interpreted as a representation that the cited publications are material, that an exhaustive search has been conducted, or that no other relevant information exists. Nor shall the citation of any publication herein be construed per se as a representation that such publication is prior art. Moreover, Applicants understand that the Examiner will make an independent evaluation of the cited publications.

Under 37 CFR § 1.97(b)(3), no additional costs are believed to be due in connection with the filing of this disclosure. If, however, a first Office Action on the merits issues in this application bearing a mailing date prior to the date of this Information Disclosure Statement, please charge the appropriate fee as required under 37 CFR §1.17(p) to our Deposit Order Account No. 12-0080.

> Respectfully submitted, LAHIVE & COCKFIELD, LLP

istration No. 52,568

28 State Street Boston, MA 02109 (617) 227-7400

Date: November 3, 2004

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Enclosures

PTO/SB/08a/b (08-03) Approved for use through 07/31/2006. OMB 0651-0031

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Complete if Known stitute for form 1449A/B/PTO Application Number 10/718,765 INFORMATION DISCLOSURE Filing Date November 21, 2003 STATEMENT BY APPLICANT First Named Inventor Kaddurah-Daouk, Rima 1639 Art Unit (Use as many sheets as necessary) **Examiner Name** Not Yet Assigned 8 AVZ-001CPUSCN2 1 Sheet of Attorney Docket Number

			U.S. PA	TENT DOCUMENTS	
Examiner Initials*	Cita	Document Number	Publication Date	Name of Patentee or	Pages, Columns, Lines, Where
	Cite No.1	Number-Kind Code <sup>2</sup> ( if known)	MM-DD-YYYY	Applicant of Cited Document	Relevant Passages or Relevant Figures Appear
	A1	5,091,404	02-25-1992	Elgebaly, S.A.	
	A2	5,321,030	06-14-1994	Kaddurah-Daouk, R., et al.	
	А3	5,324,731	06-28-1994	Kaddurah-Daouk, R., et al.	
	A4	5,492,930	02-20-1996	Coffin, V.L.	
	A5	5,676,9768	10-14-1997	Teicher, B.A., et al.	
	A6	5,741,661	04-21-1998	Goldin, S.M., et al.	
	A7	6,169,115	01-02-2001	Kaddurah-Daouk, R., et al.	

		FOREI	GN PATENT	DOCUMENTS		
Examiner	Cite	Foreign Patent Document	Publication	Name of Patentee or	Pages, Columns, Lines,	
Initials*	No.1	Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>5</sup> (if known)	Date MM-DD-YYYY	Applicant of Cited Document	Where Relevant Passages or Relevant Figures Appear	T⁵
	A8	WO 90/09192	08-23-1990	Massachusetts Institute of		
	100	WO 00/00450	05 00 4000	Technology (US)		$\vdash$
	A9	WO 92/08456	05-29-1992	Amira Inc. (US)		
	A10	WO 94/16687	08-04-1994	University of Pennsylvania (US)		
	A11	WO 94/17794 A1	08-18-1994	Jennings, S.A. (GB)		

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	A12	Annesley, T., et al., "Cyclocreatine Phosphate as a Substitute for Creatine Phosphate in Vertebrate Tissue. Energetic Considerations," <i>Biochem. Biophys. Res. Commun.</i> , 1977; 74:185-90.					
	A13	Annesley, T., et al., "Formation and Utilization of Novel High Energy Phosphate Reservoirs in Ehrlich Ascites Tumor Cells," J. Biol. Chem., 1978; 253(22):8120-5.					
	A14	Beal, M., "Aging, Energy, and Oxidative Stress in Neurodegenerative Diseases," <i>Ann. Neurol.</i> , 1995; 38:357-66.					

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Sul	Substitute for form 1449A/B/PTO			Complete if Known		
				Application Number	10/718,765	
11	NFORMATION	1 DI	SCLOSURE	Filing Date	November 21, 2003	
S	STATEMENT E	BY /	APPLICANT	First Named Inventor	Kaddurah-Daouk, Rima	
1				Art Unit	1639	
ĺ	(Use as many she	eets as	necessary)	Examiner Name	Not Yet Assigned	
Sheet	2	of	8	Attorney Docket Number	AVZ-001CPUSCN2	

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	B1	Beal, M., "Does Impairment of Energy Metabolism Result in Excitotoxic Neuronal Death in Neurodegenerative Illnesses?" <i>Ann. Neurol.</i> , 1992; 31:119-30.	
	B2	Beal, M. et al., "Age-Dependent Striatal Excitotoxic Lesions Produced by the Endogenous Mitochondrial Inhibitor Malonate," J. Neurochem., 1993; 61:1147-50.	
	ВЗ	Bertolini, et al., Chemical Abstracts AN 1982:49622.	
	B4	Brady, S., et al., "Nerve-Specific Enolase and Creatine Phosphokinase in Axonal Transport: Soluble Proteins and the Axoplasmic Matrix," <i>Cell</i> , 1981; 23:515-23.	
	B5	Brouillet, E., et al., "Chronic Mitochondrial Energy Impairment Produces Selective Striatal Degeneration and Abnormal Choreiform Movements in Primates," PNAS, 1995; 92:7105-9.	
	В6	Browne, S., <i>et al.</i> , "Oxidative Damage and Metabolic Dysfunction in Huntington's Disease: Selective Vulnerability of the Basal Ganglia," <i>Ann. Neurol.</i> , 1997; 41:646-53.	
	В7	Burbaeva, G.S., et al., "Decreased Level of Immunoreactive Phosphokinase BB Isoenzymes in the Brain of Patients with Schizophrenia and Senile Dementia of the Alzheimer Type," Zh. Nevropatol. Psikhiatr Im S S Korsakova, 1990; 90(7):85-7.	
	В8	Cadoux-Hudson, T., et al., "Imaging of Human Brain Creatine Kinase Activity in Vivo," FASEB J., 1989; 3:2660-6.	

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11	<b>NFORMATION</b>	I DI	SCLOSURE	Filing Date	November 21, 2003	
l s	TATEMENT E	3Y /	APPLICANT	First Named Inventor	Kaddurah-Daouk, Rima	
				Art Unit	1639	
	(Use as many sh	eets as	s necessary)	Examiner Name	Not Yet Assigned	
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	C1	Carter, A.J., et al., "Preincubation with creatine enhances levels of creatine phosphate and prevents anoxic damage in rat hippocampal slices," <i>J Neurochem.</i> 1995; 64(6):2691-9.	
	C2	Chandler, W., et al., "Regional Creatine Kinase, Adenylate Kinase, and Lactate Dehydrogenase in Normal Canine Brain," <i>Stroke</i> , 1988; 19:251-5.	
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	C4	De Leon, M., et al., "Identification of Transcriptionally Regulated Genes After Sciatic Nerve Injury," J. Neurosci. Res., 1991; 29:437-48.	
<u> </u>	C5	Erecinska, M., et al., "ATP and Brain Function," J. Cerebr. Bloof Flow and Metabolism, 1989; 9:2-19.	
	C6	Friedhoff, A., et al., "Creatine Kinase Isoenzyme Associated with Synaptosomal Membrane and Synaptic Vesicles," <i>Life Sci.</i> , 1977; 20:867-74.	
	C7	Goodman & Gilman, The Pharmcological Basis of Therapeutics," 1980, 6 <sup>th</sup> Ed. (MacMillan Pub.); 5-10.	
	C8	Griffiths, G., et al., "Accumulation of Analog of Phosphocreatine in Muscle of Chicks Fed 1-Carboxymethyl-2-iminoimidazolidine (Cyclocreatine)," J. Biol. Chem., 1976; 251(7):2049-54.	

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Sub	ostitute for form 1449A/B/PT	0		Complete if Known		
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l IN	<b>NFORMATION</b>	1 DI	SCLOSURE	Filing Date	November 21, 2003	
l s	TATEMENT B	3Y /	APPLICANT	First Named Inventor	Kaddurah-Daouk, Rima	
				Art Unit	1639	
	(Use as many sh	eets as	s necessary)	Examiner Name	Not Yet Assigned	
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	D1	Gu, M., et al., "Mitochondrial Defect in Huntington's Disease Caudate Nucleus," Ann. Neurol., 1996; 39:385-9.	
	D2	Gurney, M., <i>et al.</i> , "Motor Neuron Degeneration in Mice That Express a Human Cu,Zn Superoxide Dismutase Mutation," <i>Science</i> , 1994; 264:1772-5.	
	D3	Hemmer, W., et al., "Functional Aspects of Creatine Kinase in Brain," Dev. Neuroscience, 1993; 15:249-260.	
	D4	Hagenfeldt, L., et al., "Creatine Treatment in MELAS," Muscle and Nerve. 1994; 10:1236-7.	
	D5	Hemmer, W., et al., "Creatine Kinase Isoenzymes in Chicken Cerebellum: Specific Localization of Brain-type Creatine Kinase in Bergmann Glial Cells and Muscle-type Creatine Kinase in Purkinje Neurons," Eur. J. Neuroscience, 1994; 6:538-49.	
	D6	Henshaw, R., et al., "Malonate Produces Striatal Lesions by Indirect NMDA Receptor Activation," Brain Research, 1994; 647:161-6.	
	D7	Hertz, L., et al, "Energy Metabolism at the Cellular Level of the CNS," Can. J. Physiol. Pharmacol., 1992; 70:S145-57.	
	D8	Ito, M., "The Cellular Basis of Cerebellar Plasticity," Corr. Opin. Neurobiol., 1991; 1:616-20.	
	D9	Jenkins, B., et al., "Evidence for Impairment of Energy Metabolism in Vivo in Huntington's Disease Using Localized 1H NMR Spectroscopy," <i>Neurology</i> , 1993; 43:2689-95.	

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	E2	Lillie, J., et al., "Cyclocreatine (1-Carboxymethyl-2-iminoimidazolidine) Inhibits Growth of a Broad Spectrum of Cancer Cells Derived from Solid Tumors," Cancer Res., 1993; 53:3172-8.	
	E3	Lim, L., et al., "Neurone-Specific Enolase and Creatine Phosphokinase are Protein Components of Rat Brain Synaptic Plasma Membranes," J. Neurochem., 1983; 41:1177-82.	
	E4	LoPresti, P., et al., "Direct Determination of Creatine Kinase Equilibrium Constants with Creatine or Cyclocreatine as Substrate," Biochem. Biophys. Acta., 1989; 998:317-20.	
	E5	Lowe, G., et al., "Evidence for an Associative Mechanism in the Phosphoryl Transfer Step Catalyzed by Rabbit Muscle Creatine Kinase," <i>J. Biol. Chem.</i> , 1980; 225(9):3944-51.	
	E6	Maker, H., et al., "Regional Changes in Cerebellar Creatine Phosphate Metabolism During Late Maturation," Exp. Neurol., 1973; 38:295-300.	
	E7	Manos, P., et al., "Creatine Kinase Activity in Postnatal Rat Brain Development and in Cultured Neurons, Astrocytes, and Oligodendrocytes," <i>J. Neurochem.</i> , 1991; 56:2101-7.	
	E8	Marletta, M., et al., "Affinity Labeling of Creatine Kinase by N-(2,3-Epoxypropyl)-N-amidinoglycine," J. Biol. Chem., 1979; 254(6):1879-86.	
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<sup>\*</sup>EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

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		_		Application Number	10/718,765	
11	NFORMATION	1 DI	SCLOSURE	Filing Date	November 21, 2003	
S	TATEMENT E	3Y /	APPLICANT	First Named Inventor	Kaddurah-Daouk, Rima	
				Art Unit	1639	
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Sheet	6	of	8	Attorney Docket Number	AVZ-001CPUSCN2	

	U.S. PATENT DOCUMENTS						
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Examiner Initials*	Cite No. <sup>1</sup>	Number-Kind Code <sup>2</sup> ( if known)	MM-DD-YYYY	Applicant of Cited Document	Relevant Passages or Relevant Figures Appear		

	FOREIGN PATENT DOCUMENTS							
Examiner Initials*	Cite No.1	Foreign Patent Document  Country Code <sup>3</sup> -Number <sup>4</sup> -Kind Code <sup>5</sup> (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T⁵		

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		NON PATENT LITERATURE DOCUMENTS	
Examiner Initials	Cite No.1	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T²
	F1	Molloy, G., et al., "Rat Brain Creatine Kinase Messenger RNA Levels are High in Primary Cultures of Brain Astrocytes and Oligodendrocytes and Low in Neurons," J. Neurochem., 1992; 59:1925-32.	
	F2	National Library of Medicine: IGM Metathesaurus Information Screen - Nervous System Diseases definitions and related terms.	
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	F4	Oblinger, M., et al., "Cytotypic Differences in the Protein Composition of the Axonally Transported Cytoskeleton in Mammalian Neurons," J. Neurol., 1987; 7(2):453-62.	
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	F8	Roberts, J., et al., "Higher Homolog and N-Ethyl Analog of Creatine as Synthetic Phosphagen Precursors in Brain, Heart, and Muscle, Repressors of Liver Amidinotransferase, and Substrates for Creatine Catabolic Enzymes," J. Biol. Chem., 1985; 260(25):13502-8.	

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Sut	Substitute for form 1449A/B/PTO			Complete if Known		
				Application Number	10/718,765	
11	<b>NFORMATION</b>	I DI	SCLOSURE	Filing Date	November 21, 2003	
S	TATEMENT B	3Y /	APPLICANT	First Named Inventor	Kaddurah-Daouk, Rima	
				Art Unit	1639	
	(Use as many sheets as necessary)			Examiner Name	Not Yet Assigned	
Sheet	7	of	8	Attorney Docket Number	AVZ-001CPUSCN2	

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	G1	Roberts, J., et al., "Synthesis and Accumulation of an Extremely Stable High-Energy Phosphate Compound by Muscle, Heart, and Brain of Animals Fed the Creatine Analog, 1-Carboxyethyl-2-iminoimidazolidine (Homocyclocreatine)," <i>Arch. Biochem. Biophys.</i> , 1983; 220(2):563-71.	
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	G4	Schiffmann, R., et al., "Childhood Ataxia with Diffuse Central Nervous System Hypomyelination," Ann. Neurol., 1994; 35:331-40.	
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	H1	Stadhouders, A., et al., "Mitochondrial Creatine Kinase: A Major Constituent of Pathological Inclusions Seen in Mitochondrial Myopathies," PNAS, 1994; 91(11):5089-93.					
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